Remarks

Claims 1-5 and 30 are pending, with claims 8, 9, 16, 21, 22, 25-27, 29 and 31 having been withdrawn. Claims 1-5, 30 and certain of the withdrawn claims have been amended to clarify the claim language. Support for the claim amendments is found in the claims as filed and throughout the specification.

No new matter has been added.

Election

Applicant affirms the election of Group I claims and SEQ ID NOs: 16, 18 and 20 for prosecution.

Rejection Under 35 U.S.C. § 101

The Examiner rejected claims 1-5 and 30 under 35 U.S.C. § 101 as directed to non-statutory subject matter.

Applicant respectfully disagrees with the basis for the rejection, since oligonucleotides are not products of nature. However, to facilitate allowance of the claims, Applicant has amended the claims to recite that the oligonucleotides are synthetic.

Accordingly, Applicant respectfully requests withdrawal of the rejection of the claims under 35 U.S.C. § 101.

Rejection Under 35 U.S.C. § 102

1. The Examiner rejected claims 1 and 2 under 35 U.S.C. § 102(b) as anticipated by Von Knebel-Doberitz (US 6,027,891). Applicant respectfully traverses the rejection.

The Examiner alleges that the claims are anticipated because Von Knebel-Doberitz provides sequences (SEQ ID NOs:4 and 22) that are complementary to SEQ ID NO:20 of the instant application. Applicant asserts that the disclosure of a sequence complementary to an oligonucleotide sequence should not destroy the novelty of the claimed invention. The nucleotide sequences of Von Knebel-Doberitz and the claimed oligonucleotides of Applicant are not the same due to the aforementioned complementarity. The use of the molecules of Von Knebel-Doberitz would not produce the same result as the use of Applicant's oligonucleotides.

2. The Examiner rejected claims 1 and 2 under 35 U.S.C. § 102(e) as anticipated by Anthony (US 2004/0214302 A1).

The Examiner alleges that the claims are anticipated because Anthony provides SEQ ID NO:95, which is alleged to contain the exact sequence of SEQ ID NO:20 of the instant application, with additional 5' and 3' sequences.

Applicant has amended the claims to recite that the claimed oligonucleotide comprises a NASBA P1 primer. As is clearly stated in the specification (see, e.g., paragraphs [0005] and [0012] of the published application), the designation of an oligonucleotides as a "NASBA P1 primer" requires the presence of a promoter functionality at the 5' end of the primer. Applicant asserts that SEQ ID NO:95 of Anthony does not have the required promoter functionality of a NASBA P1 primer.

3. The Examiner rejected claims 1 and 5 under 35 U.S.C. § 102(b) as anticipated by Cummins (US 5,654,416).

The Examiner alleges that the claims are anticipated because Anthony provides SEQ ID NO:36, which is alleged to correspond to SEQ ID NO:18 of the instant application, with additional 5' and 3' sequences.

Applicant has amended claim 1 to recite that the oligonucleotide, when comprising SEQ ID NO:18, is a molecular beacon probe. The designation of an oligonucleotide as a molecular beacon probe requires the presence of fluorescent and quencher moieties, plus complementary non-target sequences capable of forming a step duplex (see, e.g., paragraphs [0019] and [0020] of the published application).

In contrast, the nucleic acid molecule that includes SEQ ID NO:36 of Cummins is a primer useful for the amplification of HPV DNA. The Cummins nucleic acid molecule does not have the functionality of a molecular beacon probe as is required in the claimed invention.

4. The Examiner rejected claims 1 and 5 under 35 U.S.C. § 102(b) as anticipated by Hendricks (WO 91/08312). Applicant respectfully traverses the rejection.

The Examiner alleges that the claims are anticipated because Hendricks provides a sequence (probe 18-4) that is complementary to SEQ ID NO:18 of the instant application, with additional 5' sequence.

As noted above in connection with the rejection over Von Knebel-Doberitz, Applicant asserts that the disclosure of a sequence complementary to an oligonucleotide sequence should not destroy the novelty of the claimed invention. The nucleotide sequence of Hendricks and the claimed oligonucleotides of Applicant are not the same due to the aforementioned complementarity. The use of the molecules of Hendricks would not produce the same result as the use of Applicant's oligonucleotides.

In view of the foregoing arguments and claim amendments, Applicant respectfully request that the Examiner withdraw the rejections of the claims as anticipated by the Von Knebel-Doberitz, Anthony, Cummins and Hendricks references.

Rejection Under 35 U.S.C. § 103

1. The Examiner rejected claims 1, 2 and 5 under 35 U.S.C. § 103 over Shimada in view of Buck. Applicant respectfully traverses the rejection.

The Examiner asserts that Shimada discloses sequence 18-3, which is alleged to correspond to SEQ ID NO:16 of the instant application, except that it is lacking two 3' nucleotides present in SEQ ID NO:16. Shimada does not teach Applicant's SEQ ID NO:16 or suggest which nucleotides should be added to sequence 18-3 to arrive at Applicant's sequence.

The Examiner also asserts that Shimada discloses sequence p818 II, which is alleged to correspond to SEQ ID NO:18 of the instant application, except that two of its nucleotides do not match SEQ ID NO:18, three 3' nucleotides of SEQ ID NO:18 are not present, and two 5' nucleotides that are not present in SEQ ID NO:18 are present in p818 II. Shimada does not teach Applicant's SEQ ID NO:16 or suggest which nucleotides should be changed, added or removed in sequence p818 II to arrive at Applicant's sequence.

Buck is concerned with selection of primers for DNA sequencing, which is not particularly relevant to the selection of NASBA primers.

Thus Shimada does not teach or suggest Applicant's sequences, nor does Buck provide the teaching that is lacking in Shimada. Therefore the combination of Shimada and Buck does not make out a *prima facie* case of obviousness.

Contrary to the Examiner's assertions, there is no motivation for one of ordinary skill in the art to specifically modify the sequences of Shimada to obtain the Applicant's claimed sequences. As stated by the Examiner, "different nucleotide sequences are structurally distinct chemical compounds and are unrelated to each other" (Office Action at page 3). If that is true with respect to deciding on whether to restrict inventions, it must also be considered for evaluating the teachings of the prior art. The Examiner has not shown where in the Shimada (or elsewhere) there is any suggestion to modify the sequences of Shimada to create "structurally distinct chemical compounds" as are now claimed.

As to the citation to In re Deuel, Applicant notes that the text of the opinion immediately following the passage cited by the Examiner states the following:

> "Similarly, a known compound **may** suggest its analogs or isomers, either geometric isomers (cis v. trans) or position isomers (e.g., ortho v. para).
>
> In all of these cases, however, the prior art teaches a specific, structurally-definable compound and the question becomes whether the prior art would have suggested **making the specific molecular modifications** necessary to achieve the claimed invention." (Emphasis added)

The passage cited by the Examiner also uses the word "may" with respect to the suggestion of the prior art.

The Examiner stated that "Since the claimed primers simply represent structural homologs, which are derived from sequences suggested by the prior art…" (Office Action at page 13). This statement was made without any apparent basis other than the hindsight-inspired views of the Examiner. Applicant respectfully disagrees that the primers are structural homologs of Shimada's sequences. More importantly, the Examiner has failed to provide a reference to the prior art in which the prior art suggests "making the specific molecular modifications necessary to achieve the claimed invention" as is required by In re Deuel.

Moreover, based on the claim amendments, Applicant's invention further differs from the combination of Shimada and Buck by requiring molecular beacon functionality. Specifically, the oligonucleotide that embodies sequence p818 II does not have the functionality required of a

molecular beacon probe. Moreover, both Shimada and Buck are silent as to the use of molecular beacon probes.

Finally, SEQ ID NO:16 is intended for use as a NASBA P2 primer for amplification of HPV mRNA, whereas Shimada is entirely concerned with a diagnostic method based on PCR amplification of HPV DNA, which simply would not make use of a NASBA P2 primer. Applicant maintains that Buck is not of relevance to the selection of NASBA primers, as is noted above.

In view of the foregoing arguments and claim amendments, Applicant respectfully request that the Examiner withdraw the rejections of the claims as obvious over the Shimada and Buck references.

2. The Examiner rejected claim 3 under 35 U.S.C. § 103 over Von Knebel-Doberitz in view of Kievits and further in view of Yates. Applicant respectfully traverses the rejection.

As an initial matter, Applicant first notes that the Examiner has incorrectly stated that Von Knebel-Doberitz teach "an oligonucleotide comprising the instant SEQ ID NO:20". Office Action at page 14. As noted above, SEQ ID NOs:4 and 22 of Von Knebel-Doberitz contain sequences that are complementary to SEQ ID NO:20. Thus the combination of the Von Knebel-Doberitz, Kievits and Yates references does not provide the claimed invention.

One of ordinary skill in the art also would not be motivated to use a primer complementary to the Von Knebel-Doberitz sequences, for the following reasons. The method of Von Knebel-Doberitz is dependent on the use of a 5' primer that is specific for a portion of the HPV E6-E7 mRNA and a common 3' primer (also referred to as a 3' RACE primer) that is not specific for HPV. Von Knebel-Doberitz teaches that it is essential to perform the first amplification (step (c) in the claimed method) using the common 3' RACE primer in order to amplify the extreme 3' end of the transcript.

A primer comprising Applicant's SEQ ID NO:20 is not suitable for use in this method since it cannot be used in combination with a 3' RACE primer to amplify a portion of the HPV transcript. The primer embodying SEQ ID NO:20 (in combination with a suitable forward primer) results in amplification of a completely different portion of the E6-E7 mRNA, upstream of the portion amplified in the method of Von Knebel-Doberitz. As stated above, the method of Von Knebel-Doberitz is based on amplification of the extreme 3' end of the E6-E7 mRNA using a common 3' RACE primer and a 5' primer specific for E6-E7 mRNA. There is no reason whatsoever, therefore, why a skilled person would depart from the teaching of Von Knebel-Doberitz to develop a method based on amplification of a region of the E6-E7 mRNA upstream of the 5' primer used in the method of Von Knebel-Doberitz. It is contrary to the teachings of Von Knebel-Doberitz to do so.

The Examiner indicated on page 14 of the Office Action (fourth paragraph) that "Yates et al. teach a method for detecting HPV using NASBA and molecular beacon detection." Applicant assumes that this is a typographical error since Yates describes detecting HBV, not HPV.

In view of the foregoing arguments and claim amendments, Applicant respectfully request that the Examiner withdraw the rejections of the claims as obvious over the Von Knebel-Doberitz, Kievits and Yates references.

3. The Examiner rejected claim 4 under 35 U.S.C. § 103 over Shimada in view of Simpkins. Applicant respectfully traverses the rejection.

The Examiner stated that it would be obvious to modify oligonucleotide p18-3 of Shimada to include the sequence GATGCAAGGTCGATATGAG as taught by Simpkins in order to produce a "P2" primer for use in a NASBA reaction. In fact, Shimada is entirely concerned with detection of HPV by amplification of HPV genomic DNA and neither teaches nor suggests a method based on amplification of HPV mRNA. Thus, the combination of Shimada and Simpkins does not provide the claimed invention, nor would there be any motivation to combine the teachings of these references. There is additionally no motivation to

modify the nucleotide sequences disclosed by Shimada in the context of genomic DNA amplification to produce primers for amplification of HPV mRNA by NASBA.

In view of the foregoing arguments and claim amendments, Applicant respectfully request that the Examiner withdraw the rejections of the claims as obvious over the Shimada and Simpkins references.

4. The Examiner rejected claim 30 under 35 U.S.C. § 103 over Cummins in view of Leone and further in view of Kievits or Yates. Applicant respectfully traverses the rejection.

Cummins is concerned with detection of HPV by amplification of HPV genomic DNA, not mRNA. More specifically, Cummins teaches use of polymerase chain reaction to provide simultaneous amplification of two or more target nucleic acids (from two or more infectious agents) in a single reaction ("multiplexing"). There is no disclosure in Cummins of a method based on direct amplification of HPV mRNA.

In particular, SEQ ID NO:36 of Cummins, which includes SEQ ID NO:18 of the present invention, is described by Cummins as a primer useful for amplification of HPV genomic DNA. In contrast, SEQ ID NO:18 of the present application is used as a molecular beacon probed for detection of the products of a NASBA reaction that is designed to amplify HPV mRNA transcripts.

Thus the combination of references fails to provide the elements of the claimed invention. Moreover, since Cummins fails to teach a method based on amplification of HPV mRNA, Cummins provides no motivation whatsoever to switch to the NASBA methodology as taught be Leone and Kievits.

Further, a key feature of the Cummins method is the simultaneous amplification of DNAs from two or more infectious agents in a single reaction. There is no suggestion in Leone or Kievits that the NASBA technique allows such "multiplexing". To switch from use of PCR

amplification of DNA to NASBA amplification of mRNA would change the whole nature of the Cummins method.

Finally, neither Leone nor Kievits provide any motivation to modify SEQ ID NO:36 of Cummins to form a molecular beacon probe.

In view of the foregoing arguments and claim amendments, Applicant respectfully request that the Examiner withdraw the rejections of the claims as obvious over the Cummins, Leone, Kievits and Yates references.

5. The Examiner rejected claim 30 under 35 U.S.C. § 103 over Hendricks in view of Leone and further in view of Kievits or Yates. Applicant respectfully traverses the rejection.

As was noted above, probe 18-4 of Hendricks comprises the complement of SEQ ID NO:18, and therefore is not useful in Applicant's claimed invention. However, for the sake of argument and without admitting that the combination of references provides motivation to modify probe 18-4, if a person skilled in the art were to modify this probe to produce a molecular beacon probe, the result would be a molecular beacon comprising complementary sequences to SEQ ID NO:18. Thus, the combination of references does not provide the claimed invention.

Moreover, Hendricks provides no motivation for the skilled person to produce a probe of complementary sequence to probe 18-4. In addition, since none of the Leone, Kivits or Yates references is concerned with detection of HPV, these references also fail to provide any motivation for the skilled person to produce a probe comprising complementary sequence to probe 18-4 of Hendricks.

In view of the foregoing arguments and claim amendments, Applicant respectfully request that the Examiner withdraw the rejections of the claims as obvious over the Hendricks, Leone, Kievits and Yates references.

CONCLUSION

In view of the foregoing amendments and remarks, this application should now be in condition for allowance. A notice to this effect is respectfully requested. If the Examiner believes, after this amendment, that the application is not in condition for allowance, the Examiner is requested to call the Applicant's attorney at the telephone number listed below.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Respectfully submitted,
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